Nausea and Vomiting

Pharmacotherapy I

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Overview

Nausea

- unpleasant feeling with epigastrium & abdominal symptoms
- Usually occurs before vomiting

Vomiting

- An organized, autonomic response that results in the forceful expulsion of gastric contents through the mouth

Nausea and vomiting have a significant negative impact on quality of life

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Etiology

Nausea and/or vomiting may be associated with a number of conditions including gastrointestinal (Pancreatitis Hepatitis), cardiovascular, infectious, neurologic, metabolic, psychogenic processes, or pregnancy

Nausea and/or vomiting is also associated with numerous medications and noxious agents

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Iatrogenic, Toxic, and Infectious Causes

Almost any medication can cause N/V with chemotherapeutic agents being the most well known

Overdoses of alcohol, illicit drugs, and other toxins may cause acute N/V

Infectious causes usually result in acute onset N/V

- Viral gastroenteritis is very common
- Bacteria and their toxins may also be the cause

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Gastrointestinal Disorders

Acute N/V typically the result of an inflammatory process

- Appendicitis, cholecystitis, pancreatitis

Obstructions can cause acute or chronic symptoms

- Gastric outlet obstructions tend to cause intermittent N/V
- Intestinal obstructions tend to acute N/V and severe pain

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Gastrointestinal Disorders

Motility disorders

- Gastroparesis produces N/V from the inability to move food through the GI tract

The following GI disorders may have N/V associated with them, but these are not the primary symptoms

- Dyspepsia, GERD, PUD, and IBS

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CNS and Psychiatric Conditions

Conditions that increase intracranial pressure can cause N/V
- Tumor, infarct, infection

Migraine headaches often cause N/V

Patients may also experience N/V from emotional or physical stressors

N/V can also be associated with anorexia nervosa,, depression, and anxiety

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Other Conditions

Pregnancy is the most common endocrinologic cause of N/V

Metabolic causes of N/V include the following:

- Acidosis, uremia, hyperthyroidism, adrenal disorders, parathyroid disorders

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Pathophysiology

3 phases of emesis include:

Nausea

- The need to vomit

Retching

- Labored movement of the abdominal and thoracic muscles before vomiting

Vomiting

- Forceful expulsion of gastric contents through the mouth caused by GI retoperistalsis

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Pathophysiology

Areas involved in nausea and vomiting

Vomiting center

- Integrates afferent impulses from sensory centers to efferent impulses to different areas including the salivation and respiratory centers and to pharyngeal, GI, and abdominal muscles leading to vomiting

Chemoreceptor trigger zone (CTZ)

- Located in the brain and is the major chemosensory organ for emesis
- Associated with chemically-induced vomiting

GI tract

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Pathophysiology

Neurotransmitter receptors are in the vomiting center, CTZ, and GI tract

- These include cholinergic, histaminic, dopaminergic, opiate serotonergic, neurokinin, and benzodiazepine receptors

Medications, disease states, and various circumstances can cause stimulation of these receptors to cause N/V

There are antiemetic drugs that block these receptors

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3 Step Initial Evaluation

Attempt — Attempt to recognize and correct any consequences of the N/V such as dehydration or electrolyte disturbances

Try — Try to identify the underlying cause and provide specific therapies

Use — If the etiology can't be determined, use empiric therapy to treat the symptoms

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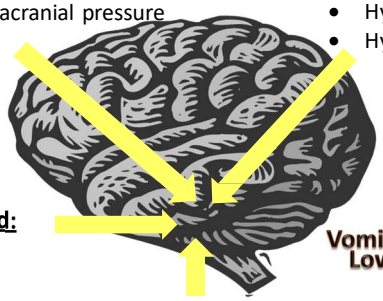
Physiologic:
Constipation
Gastric stasis
Increased intracranial pressure
Obstruction
Oral thrush

Metabolic:
Uremia
Electrolyte imbalance
- Hypercalcemia
- Hyponatremia



Treatment related:
Chemotherapy
Radiation therapy:
- GI tract or brain

Medications:
- Antibiotics
- ASA/NSAIDS
- Corticosteroids
- Initial opioid therapy

Psychological/emotional:
Anticipatory n/v
Anxiety
Fear
Suffering

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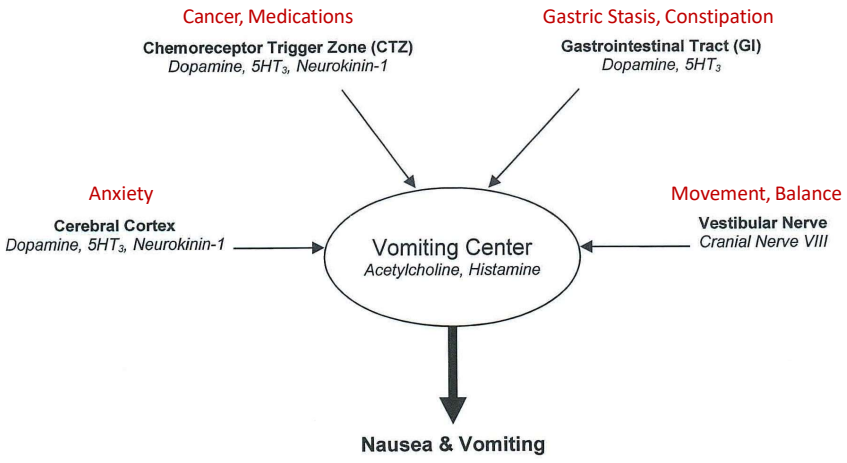

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Clinical Presentation

Simple

- Self limiting, may resolve spontaneously
- Queasiness and/or discomfort
- Only symptomatic therapy required
- May self treat

Complex

- Not relieved with antiemetics
- Fluid-electrolyte imbalance
- Persistent vomiting when pregnant
- Weight loss/fever/abdominal pain
- Usually associated with noxious agents (e.g. oncology/chemotherapy agents) or psychogenic events
- Requires work up with clinician

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Complications of Nausea and Vomiting

- Dehydration
- Electrolyte imbalances (hypokalemia)
- Esophageal tear
- Malnutrition long term

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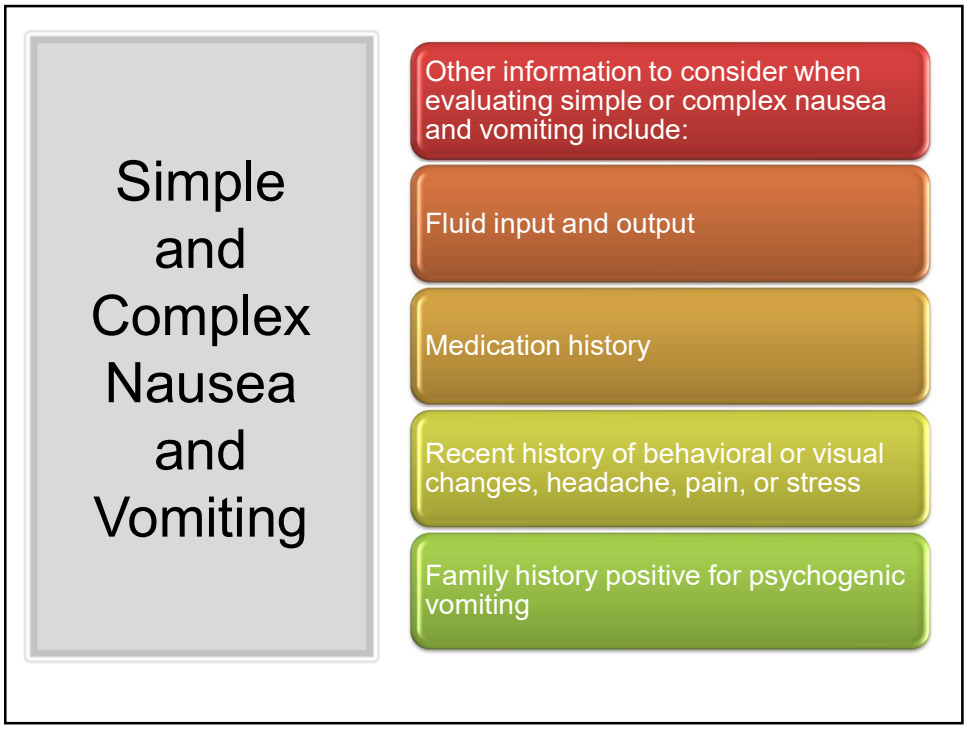

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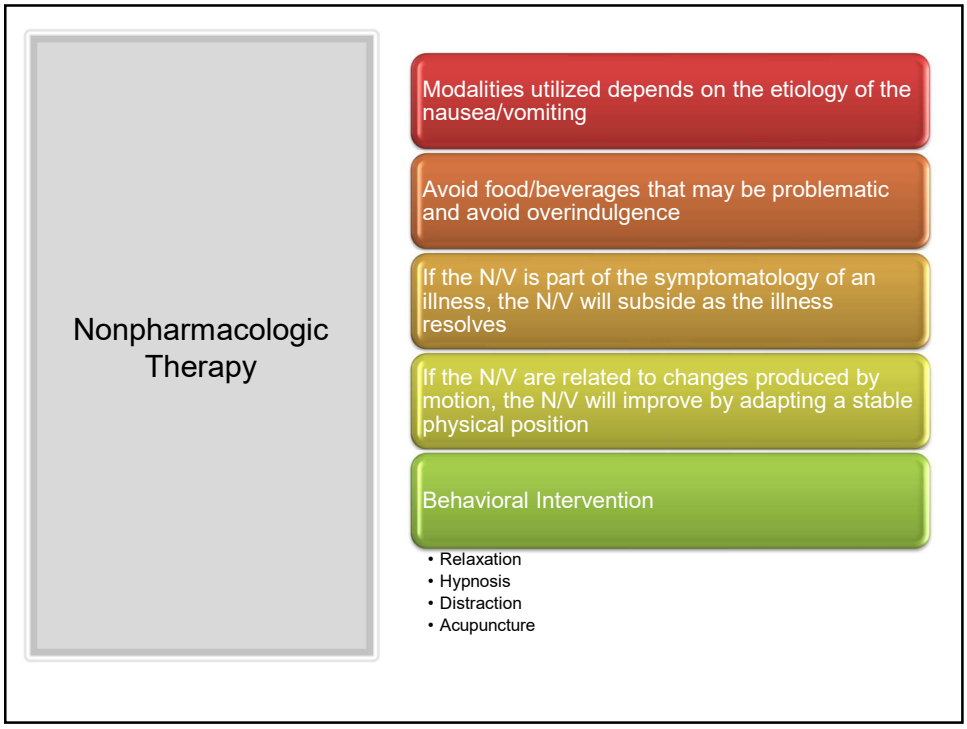

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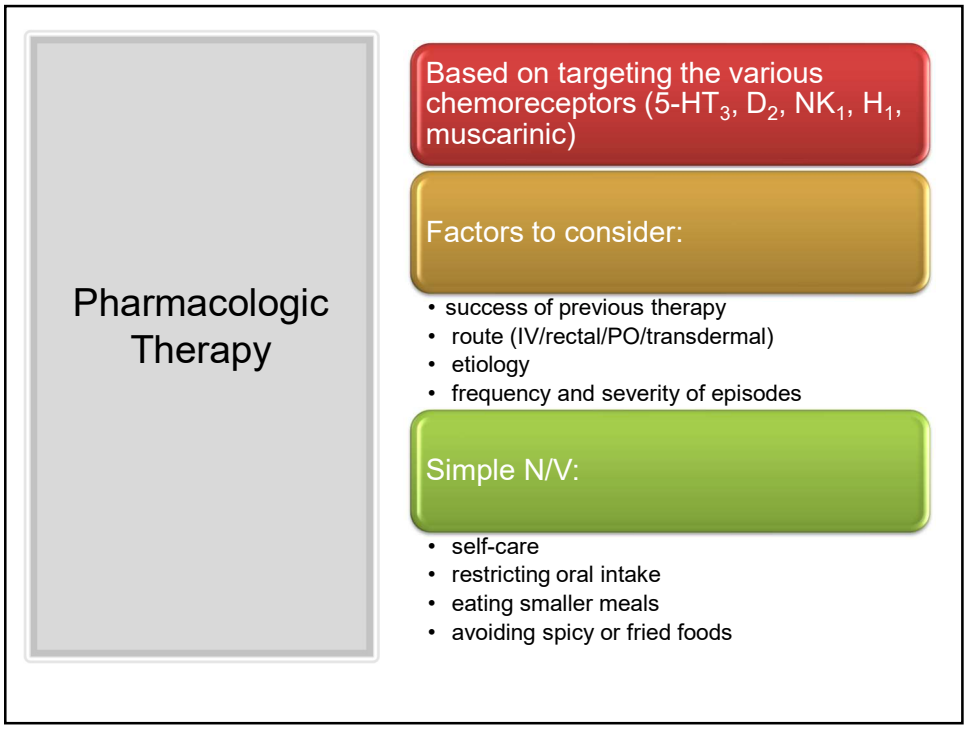

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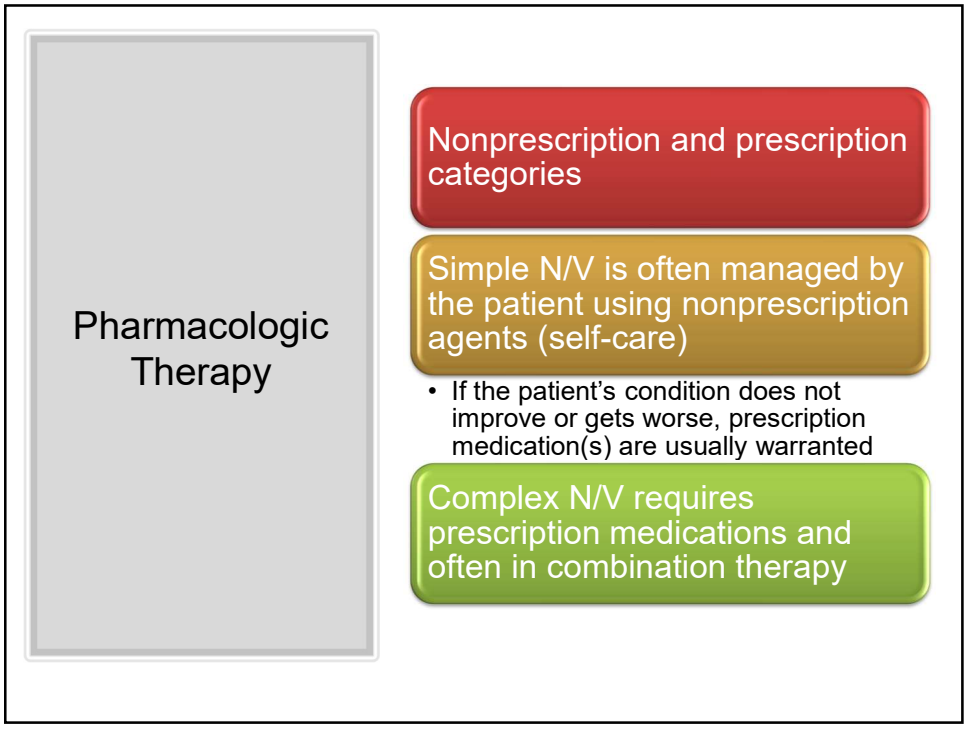

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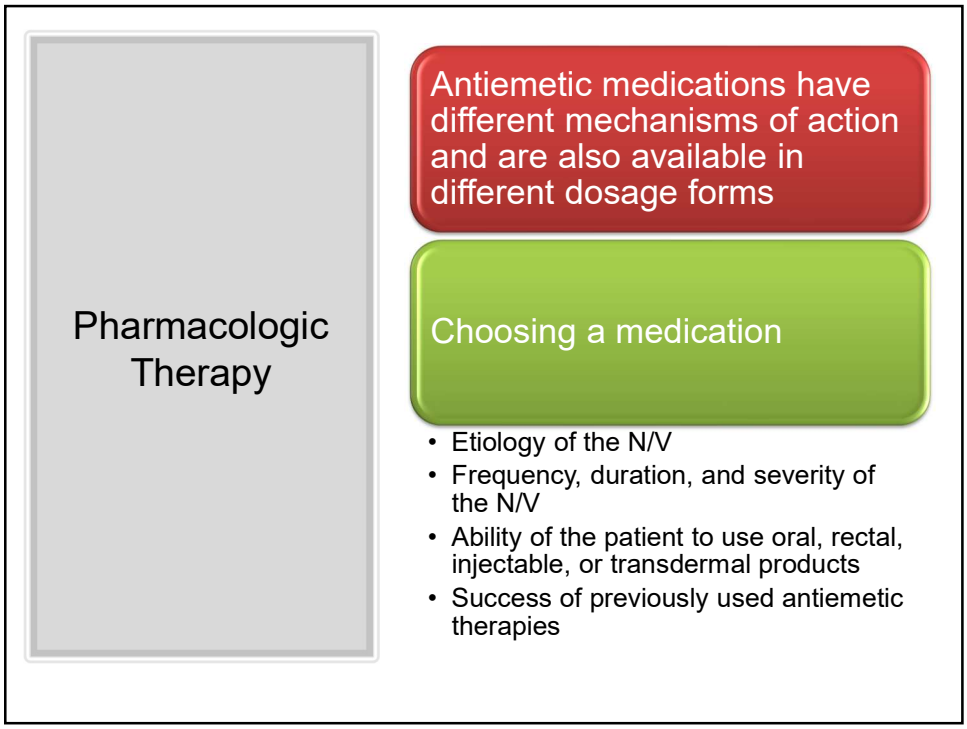

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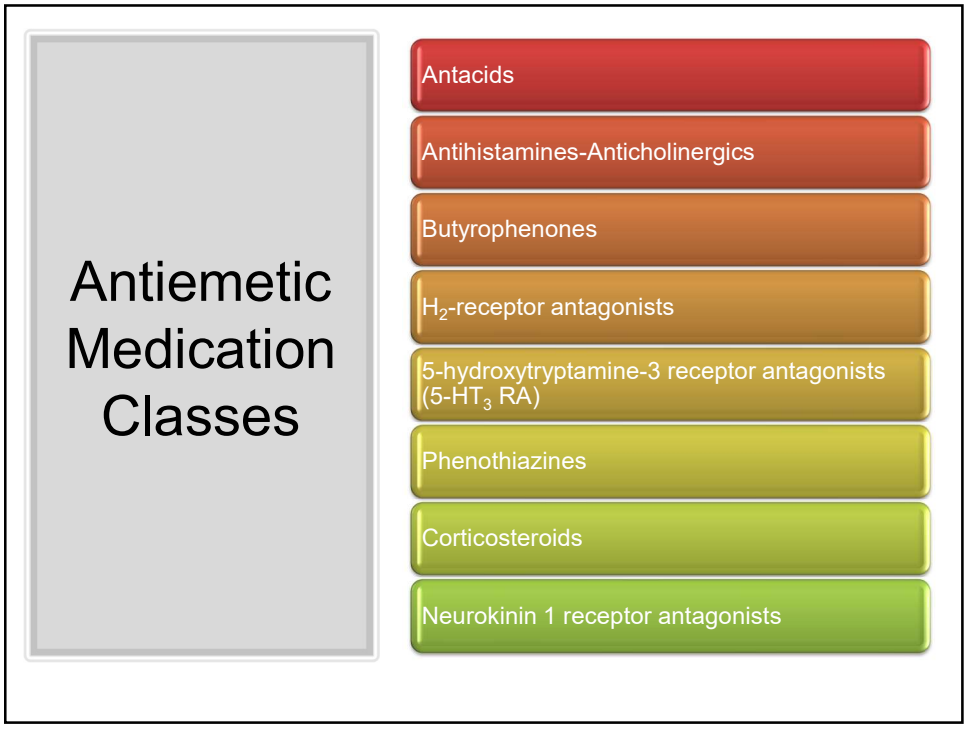

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OTC Medications

- First step for simple N/V
- Antacids
- Antihistamines
- H_2 Antagonists
- Emetrol
- Cola Syrup

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Antacids

- **Can be used to help relieve simple nausea and vomiting**
  - Work primarily through gastric acid neutralization
  - Useful in simple N/V caused by overeating or secondary to heartburn/GERD
- **MOA**
  - Neutralize hydrochloric acid in the stomach, which results in an increase in gastric pH
- **Agents**
  - Magnesium hydroxide
  - Aluminum hydroxide
  - Calcium carbonate
- **Adverse effects**
  - Diarrhea (magnesium hydroxide)
  - Constipation (aluminum hydroxide and calcium carbonate)
  - Alterations in mineral metabolism
  - Acid-base disturbances

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Antacids

Monitoring

- Periodic calcium and phosphate levels if on chronic antacid therapy

Patient counseling

- Antacids can decrease the levels of numerous other drugs including tetracyclines, digoxin, iron supplements, fluroquinolones, and ketoconazole.
  - Patients should separate antacids and other medications by at least 2 hours
- Patients with renal impairment should not use aluminum or magnesium containing antacids unless directed by their physician

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Antihistamine-Anticholinergic Drugs

Used for simple N/V associate with motion sickness

MOA

- Interrupt visceral afferent pathways that stimulate N/V
- Suppresses vestibular end-organ receptors and inhibits activation of central cholinergic pathways

Agents

- Dimenhydrinate (Dramanine)
- Diphenhydramine (Benadryl)
- Hydroxyzine (Vistaril, Atarax)
- Meclizine (Bonine, Antivert)
- Scopolamine (Transderm Scop)
- Trimethobenzamide (Tigan)

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Antihistamine-Anticholinergic Drugs

Adverse effects

- Drowsiness, confusion, blurred vision, dry mouth, urinary retention

Monitoring

- Improvement in N/V

Patient counseling

- Especially problematic in the elderly
- Increased risk of complications in those with BPH, narrow angle glaucoma, or asthma
- Avoid activities that require mental alertness until the the effects of the medication is realized
- Avoid alcohol and other CNS depressants as an additive effect may occur

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Butyrophenones

Used in palliative care and postoperative nausea and vomiting (PONV)

Not recommended as first-line therapy

MOA

- Block dopaminergic stimulation of the CTZ

Agents

- Haloperidol (Haldol)
- Droperidol (Inapsine)

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Butyrophenones

Adverse effects

- Sedation, constipation, hypotension, QT prolongation/torsade de pointes

Monitoring

- EKG prior to administration followed by cardiac monitoring 2 to 3 hours after administration

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H_2-Receptor Antagonists

Useful when N/V is related to heartburn or GERD

MOA

Competitive inhibition of histamine at H_2 receptors of gastric parietal cells which inhibits gastric acid secretion

Agents

Cimetidine (Tagamet)	Famotidine (Pepcid)	Nizatidine (Axid)	Ranitidine (Zantac)

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H_2-Receptor Antagonists

Adverse effects

- Headache, somnolence, fatigue, dizziness, constipation, diarrhea

Monitoring

- Monitor for CNS effects (rare) in those over 50 years old or in those with renal or hepatic impairment

Patient counseling

- Onset of relief is 30 to 45 minutes and duration of relief is 4 to 10 hours

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Dopamine Antagonists

- Metoclopramide
- Central blockage of CTZ
- Cholinergic prokinetic activity, promotes gastric motility
- Useful in N/V in patients with diabetic gastricparesis
- Aids in gastric emptying
- AEs: EPS, hyperprolactinemia, gynecomastia
- Use declining

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Benzodiazepines

- Lorazepam, alprazolam
- Effective in anticipatory N/V
- May inhibit impulses from cerebral cortex to vomiting center
- Considered weak antiemetic agents
- Used to prevent anxiety or N/V in pts receiving highly ematogenic chemotherapy, radiotherapy, or surgery
- Often used as adjunct agents
- Usually given orally (alpraz, loraz) or SL (loraz)
- AEs: resp. depression, sedation

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5-hydroxytryptamine-3 Receptor Antagonists

Standards of care in CINV, Post- Operative Nausea and Vomiting (PONV), and Radiation Induced Nausea and Vomiting (RINV)

MOA

Block presynaptic serotonin receptors in sensory vagal fibers in the gut wall

Agents

Dolasetron (Anzemet)	Ondansetron (Zofran)	Granisetron (Kytril)	Palonosetron (Aloxi)

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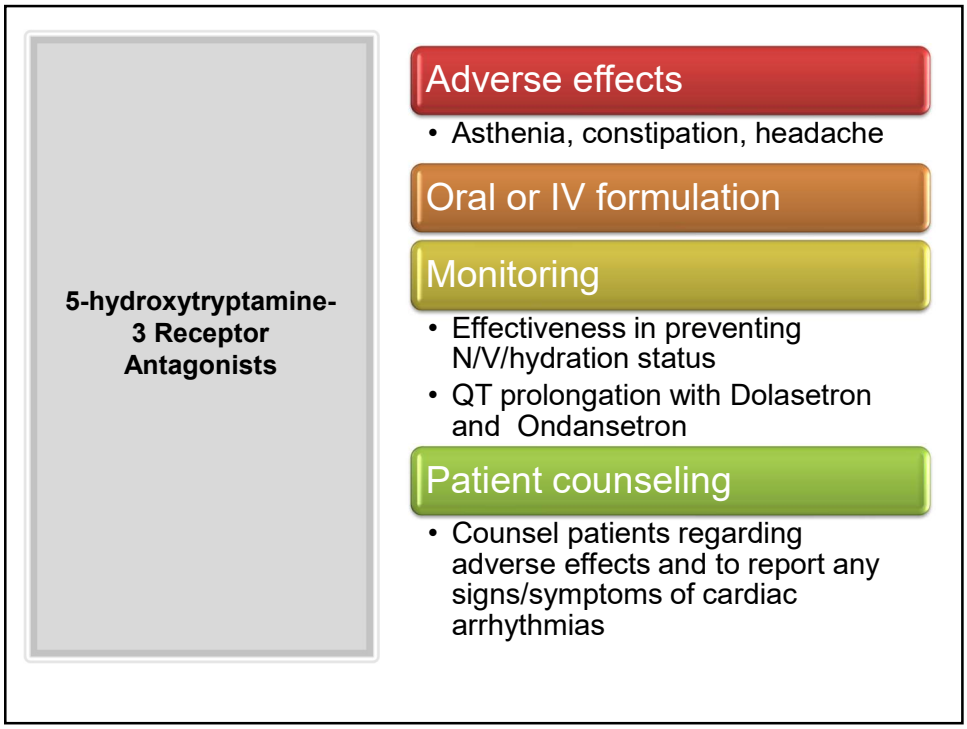

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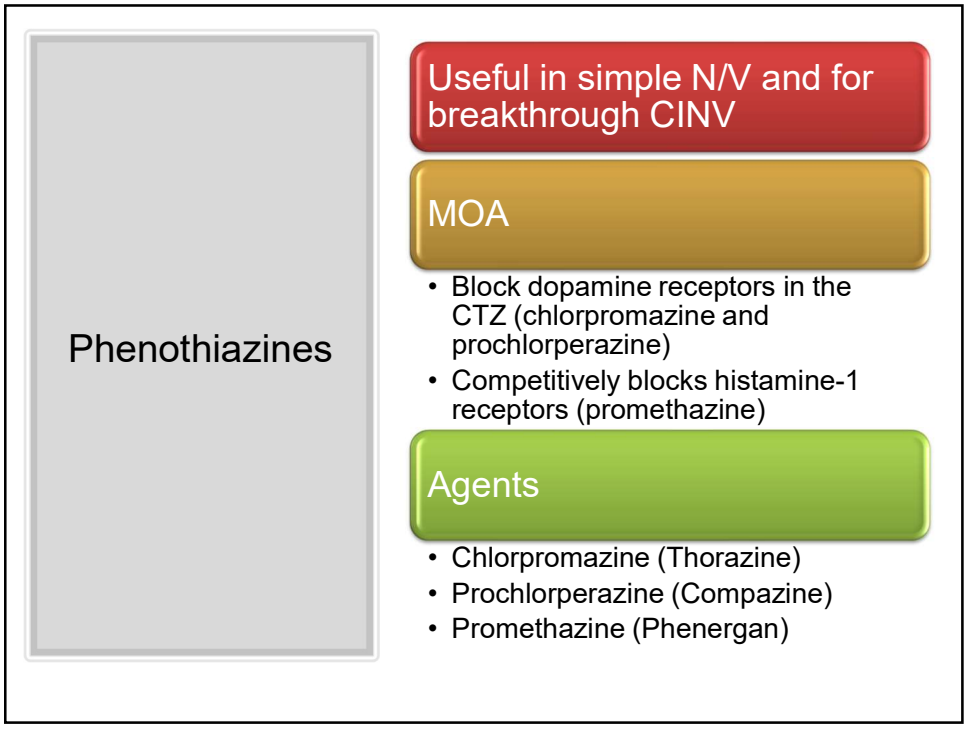

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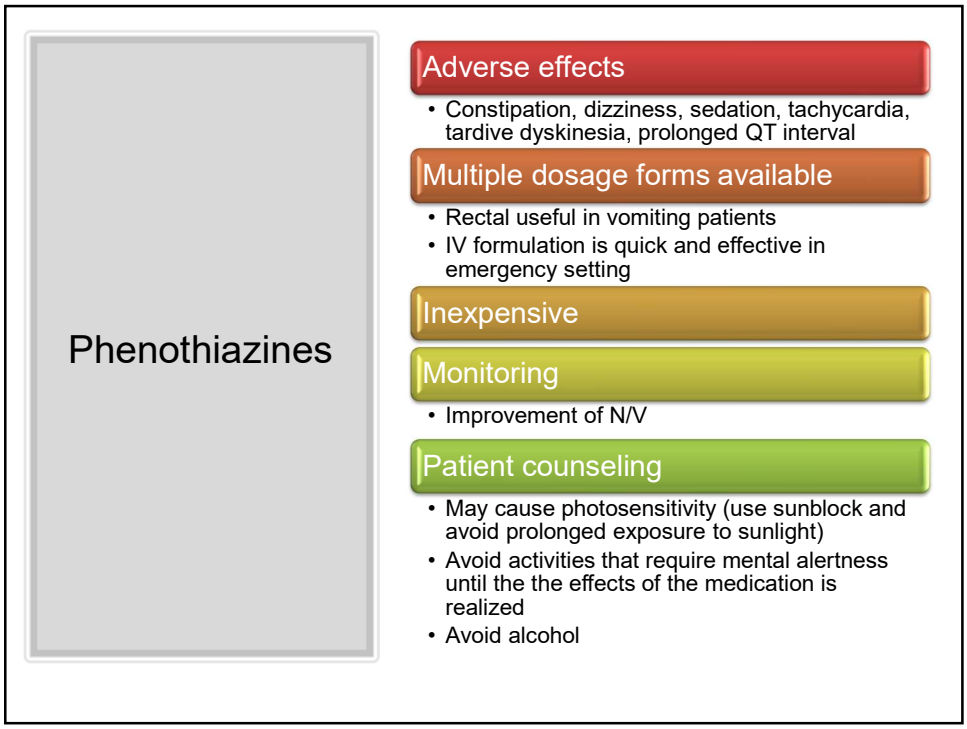

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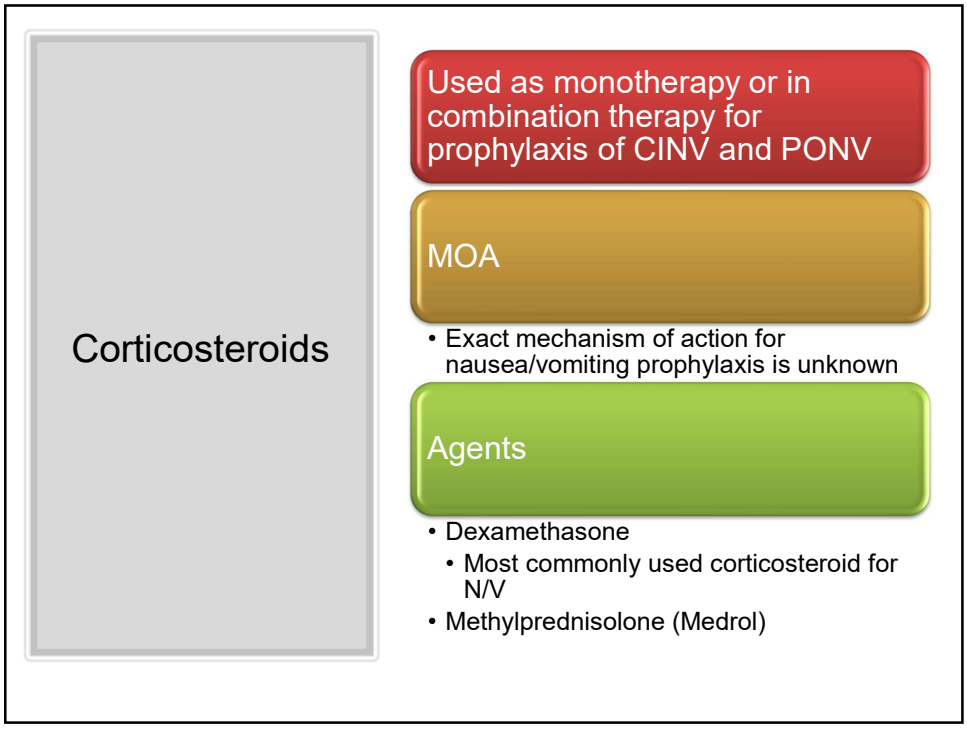

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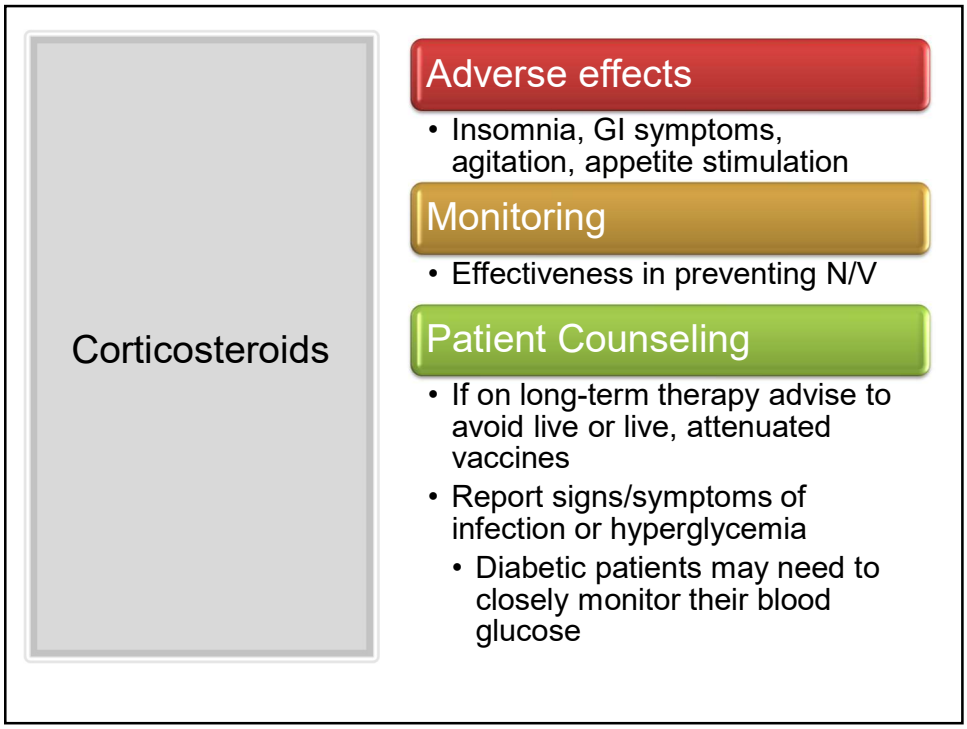

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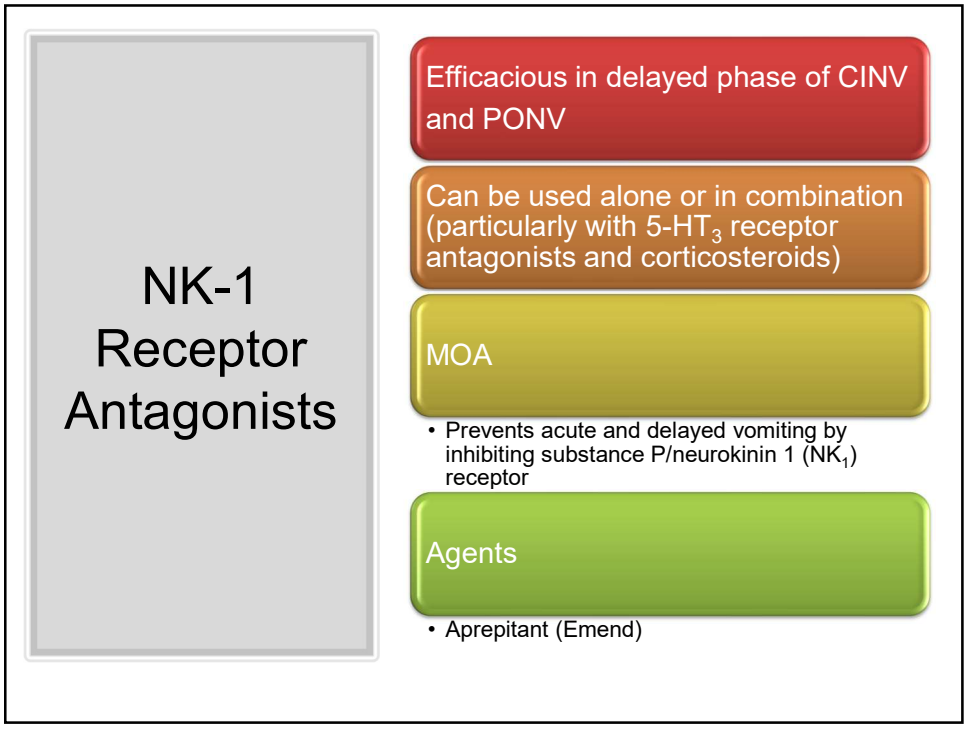

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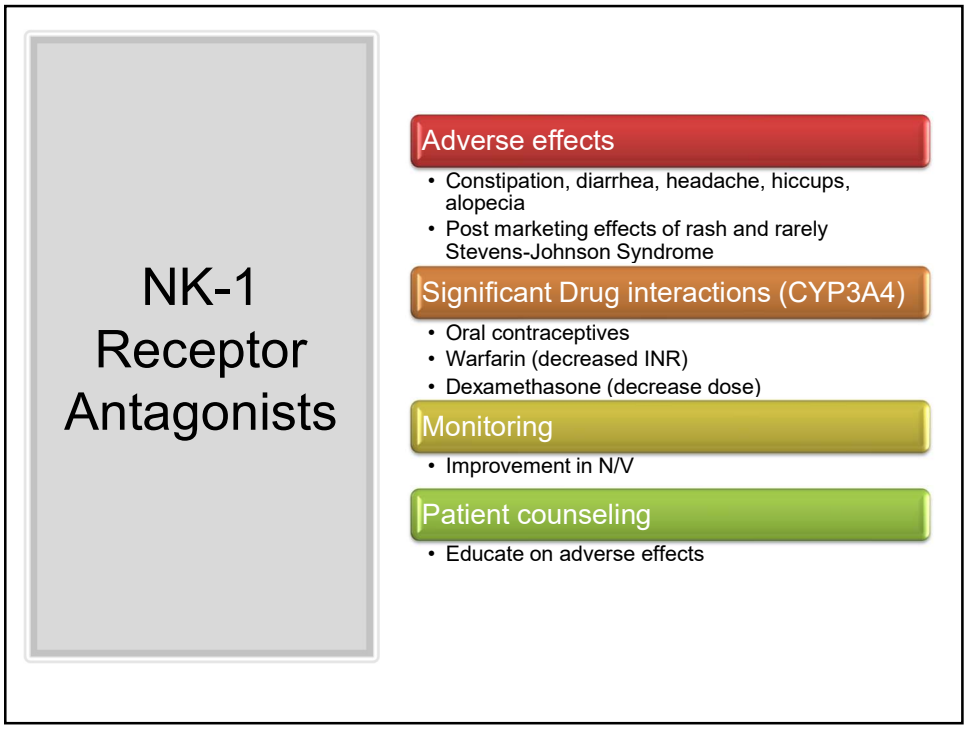

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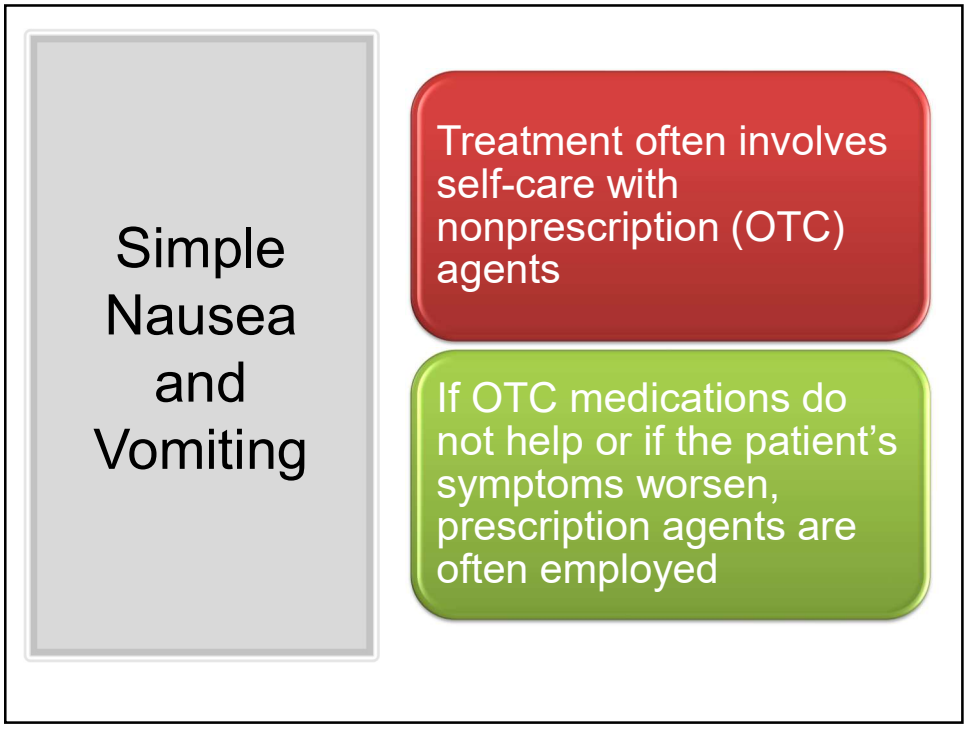

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Nausea and Vomiting

For both simple and complex nausea and vomiting, an attempt should be made to identify the etiology so that targeted therapy can be utilized

If the etiology is unknown and OTC medications are not working:

- It is reasonable to begin prescription therapy with a trial of a phenothiazine, such as prochlorperazine
- 5-HT_3RA's like ondansetron are also effective and may be better tolerated than phenothiazines, but their high cost is a concern particularly if being used long-term

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CINV

CINV: Acute (< 24h), delayed (> 24h), anticipatory, breakthrough, refractory

General Principles

- Primary goal is no N/V during emetic risk period (2 days moderate and 3 day high)
- Choice of drug based on Chemotherapy agent with highest risk, prior emetic experience, and patient specific factors
- When given in equipotent doses, oral and IV 5-HT_3-RAs are equally effective
- Consider and manage toxicities of antiemetics

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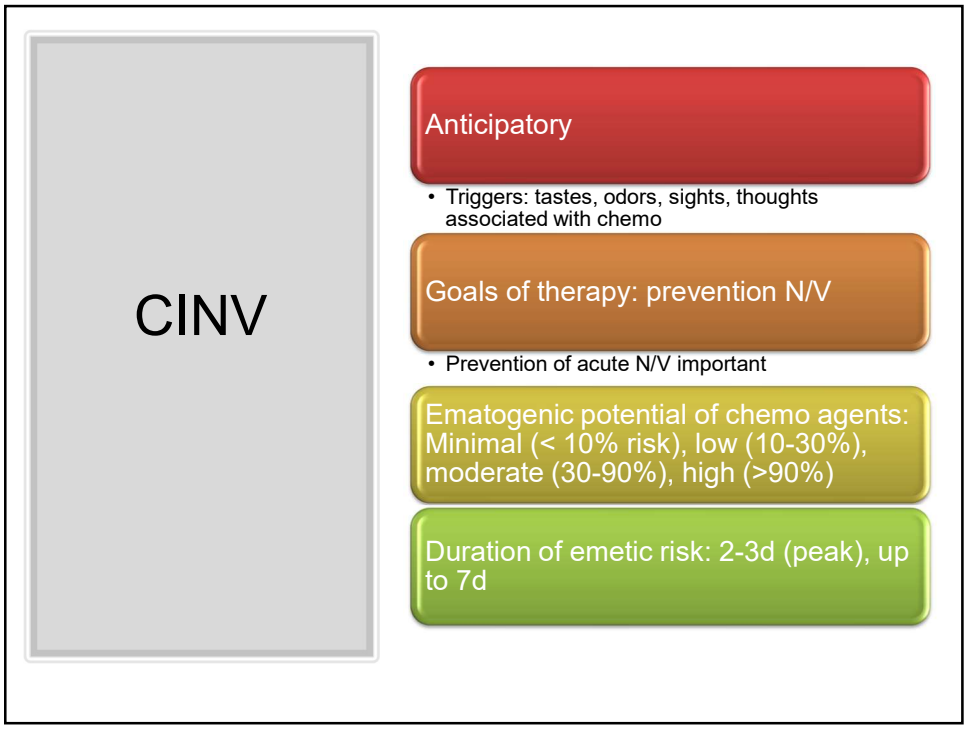

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Emetic Risk Antineoplastic Agents Administered Intravenously

High	Moderate	Low		Minimal
Carmustine Cisplatin Cyclophosphamide >1500 mg/m2 Dacarbazine Dactinomycin Mechlorethamine Streptozotocin	Azacitidine Alemtuzumab Bendamustine Carboplatin Cyclophosphamide <1500 mg/m2 Cytarabine >1000 mg/m2 Daunorubicin Doxorubicin Epirubicin Idarubicin Ifosfamide Irinotecan Oxaliplatin	5-FU Bortezomib Cabazitaxel Cytarabine <1000 mg/m2 Docetaxel Doxorubicin (liposomal) Etoposide Gemcitabine Ixabepilone Methotrexate Mitomycin Mitoxantrone Paclitaxel	Panitumumab Pemetrexed Temsirolimus Topotecan Trastuzumab	Bevacizumab Bleomycin Busulfan Cetuximab Fludarabine Pralatrexate Rituximab Vinblastine Vincristine Vinorelbine

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Table 3. Antiemetic Dosing by Chemotherapy Risk Category

Risk Category	Dosing on Day of Chemotherapy	Dosing on Subsequent Days
High emetic risk*		
NK_1 antagonist		
Aprepitant	125 mg oral	80 mg oral; days 2 and 3
Fosaprepitant	150 mg IV	
5-HT_3 antagonist		
Granisetron	2 mg oral; 1 mg or 0.01 mg/kg IV	
Ondansetron	8 mg oral twice daily; 8 mg or 0.15 mg/kg IV	
Palonosetron	0.50 mg oral; 0.25 mg IV	
Dolasetron	100 mg oral ONLY	
Tropisetron	5 mg oral; 5 mg IV	
Ramosetron	0.3 mg IV	
Corticosteroid†		
Dexamethasone	12 mg oral or IV	8 mg oral or IV; days 2-3 or days 2-4
Moderate emetic risk‡		
5-HT_3 antagonist		
Palonosetron	0.50 mg oral; 0.25 mg IV	
Corticosteroid		
Dexamethasone	8 mg oral or IV	8 mg; days 2 and 3
Low emetic risk		
Corticosteroid		
Dexamethasone	8 mg oral or IV	

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Acute CINV Prophylaxis

- Low ematogenic potential: single agent is effective (dexamethasone, metoclopramide, or 5HT3-RA, prochlorperazine, lorazepam) on day of chemo
- Moderate ematogenic potential: two antiemetic drug combination (5-HT_3 RAs on day 1, dexamethsone on day 1-3) for most regimens
- High ematogenic potential: 3 antiemetic drug combination given on day 1 of chemo (5-HT_3 RAs, dexamethsone, NK_1 RA,)
- Other option (olanzapine + 5-HT3+DEX)
- IV 5-HT_3 RAs equivalent in efficacy/Oral

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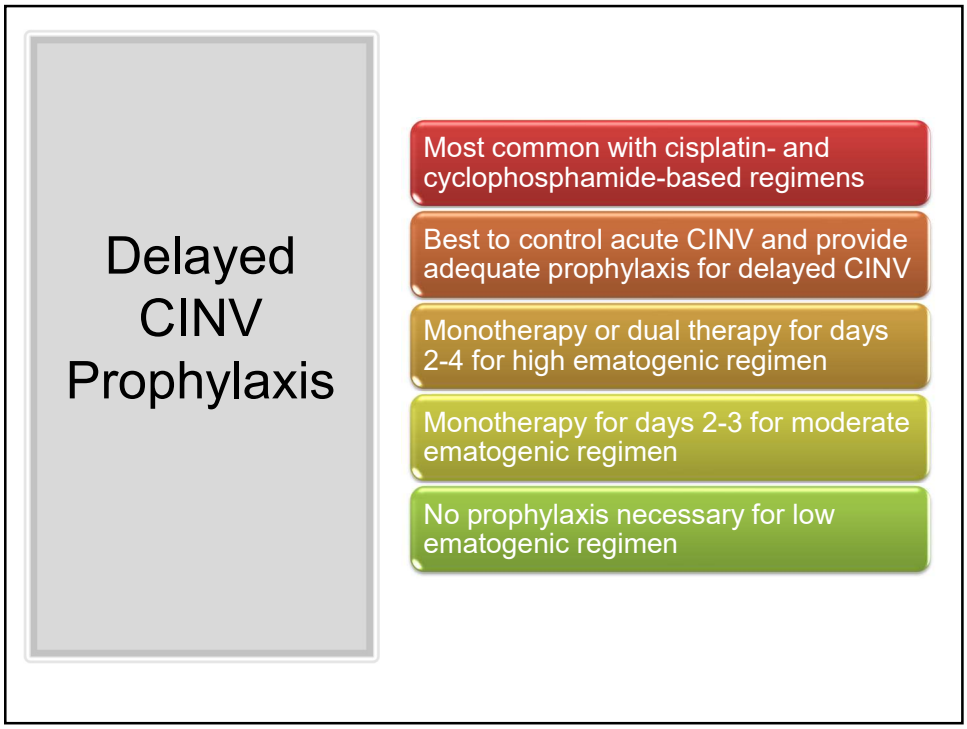

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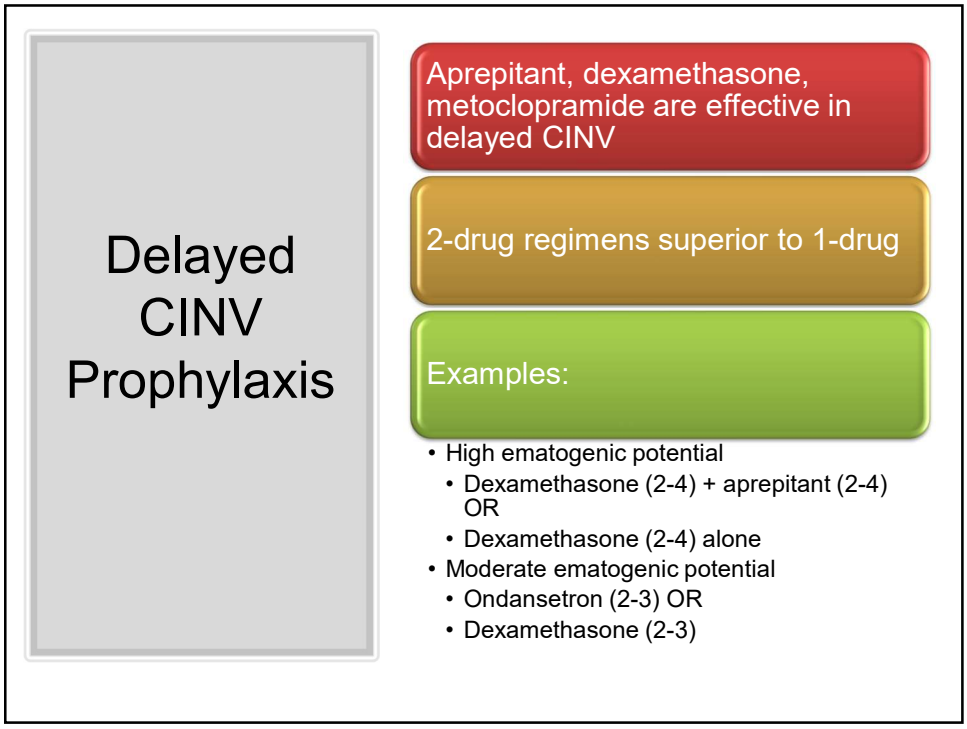

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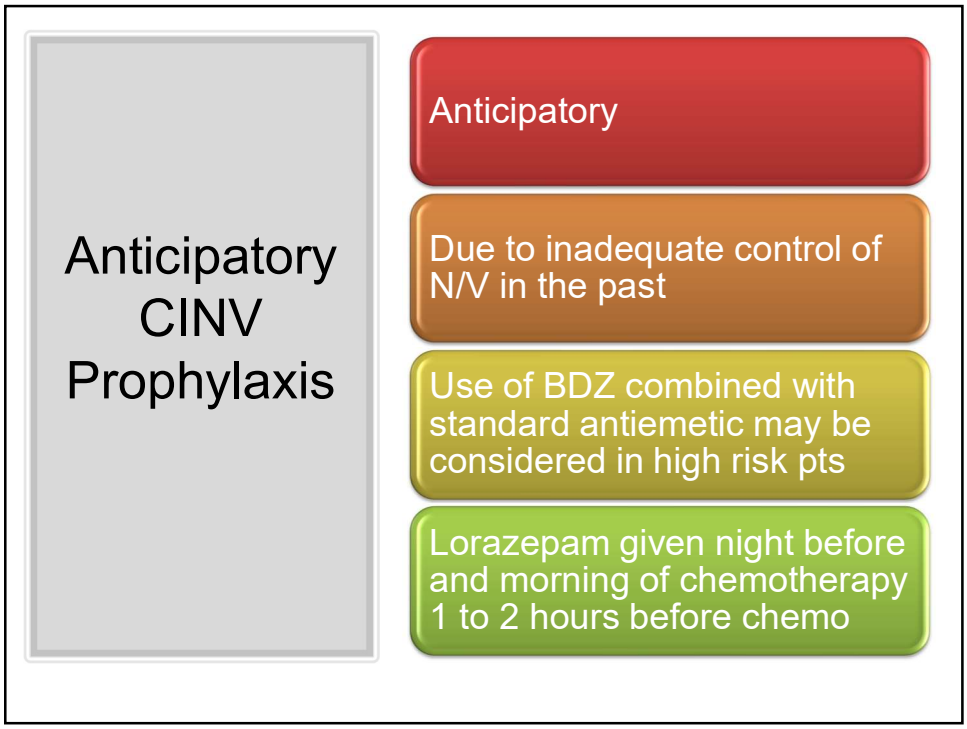

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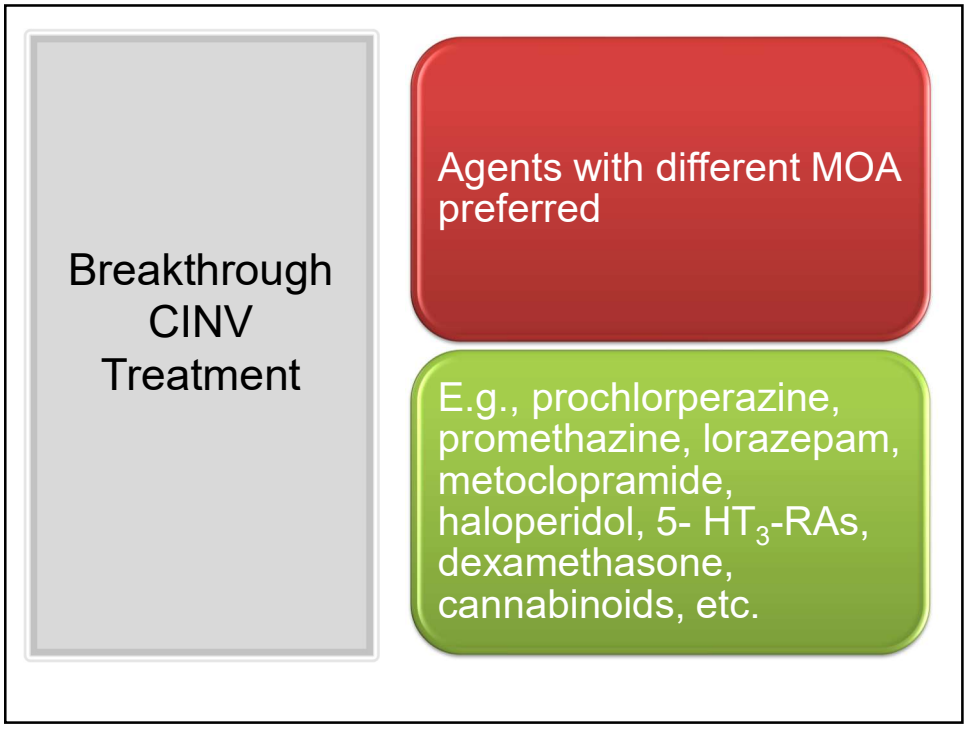

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Radiation-Induced N/V (RINV)

Incidence: 50-80%

Risk factors: combination chemotherapy, prior CINV, upper abdomen RT, radiation field size

Risk:

- Minimal: 5-HT_3 RAs, metoclopramide, or prochlorperazine may be offered as rescue
- Low: 5-HT_3 RAs either throughout RT or as needed
- Moderate: 5-HT_3 RAs prior to each fraction and dexamethasone on fractions 1-5
- High: 5-HT_3 RAs throughout RT and dexamethasone on fractions 1-5 in pts who are receiving total body irradiation

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Overview of Postoperative Nausea and Vomiting (PONV)

PONV is common and distressing to patients

General incidence of vomiting is 30%

General incidence of nausea is 50%

High-risk patients can have a PONV rate of 80%

General approach taken is to assess a patient's PONV risk, reduce baseline risks, and provide appropriate PONV prophylaxis

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Risk Factors for PONV

- Female sex
- History of PONV or motion sickness
- Nonsmoking
- Younger age (< 50 years old)
- General vs. regional anesthesia
- Use of volatile anesthetics and nitrous oxide
- Postoperative opioids
- Duration of anesthesia
- Type of surgery
  - Higher incidence with cholecystectomy, laparoscopic, gynecological)

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Apfel Simplified Risk Score

Predicts a patient's risk of PONV based on presence of 4 risk factors

Risk Factors	Points
Female Gender	1
Non-smoker	1
History of PONV	1
Postoperative Opioids	1
Sum	0 to 4

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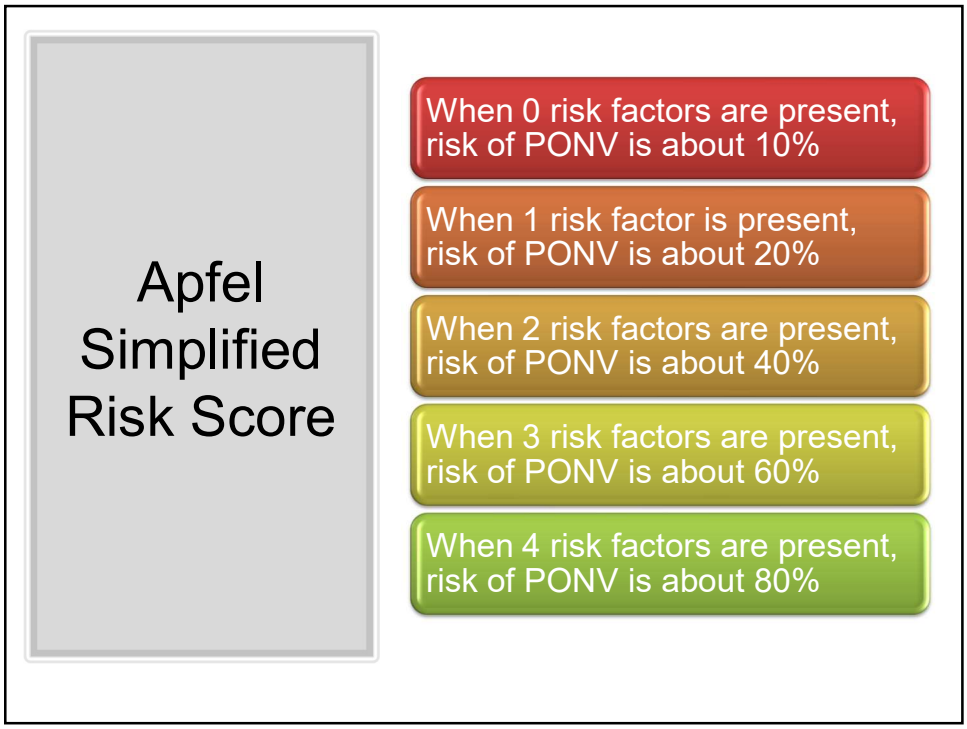

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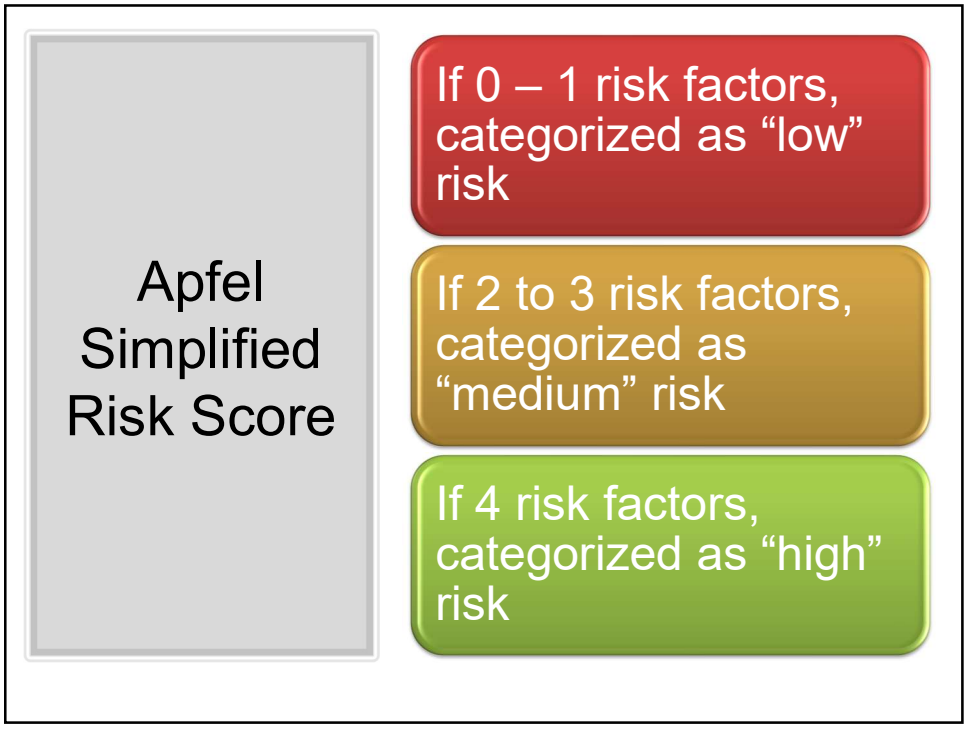

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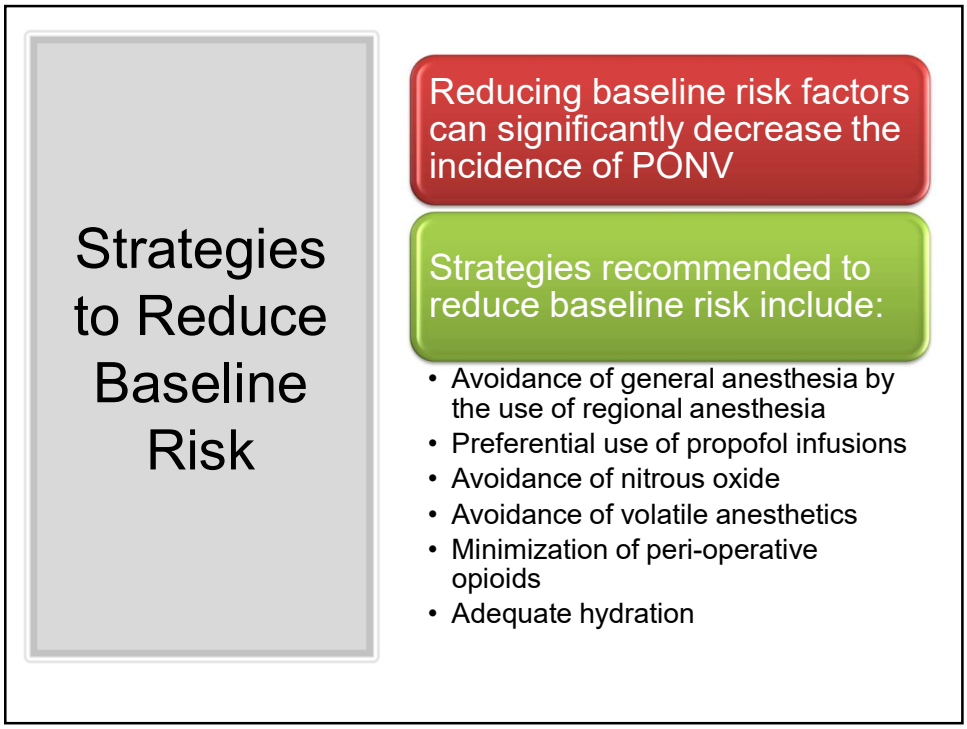

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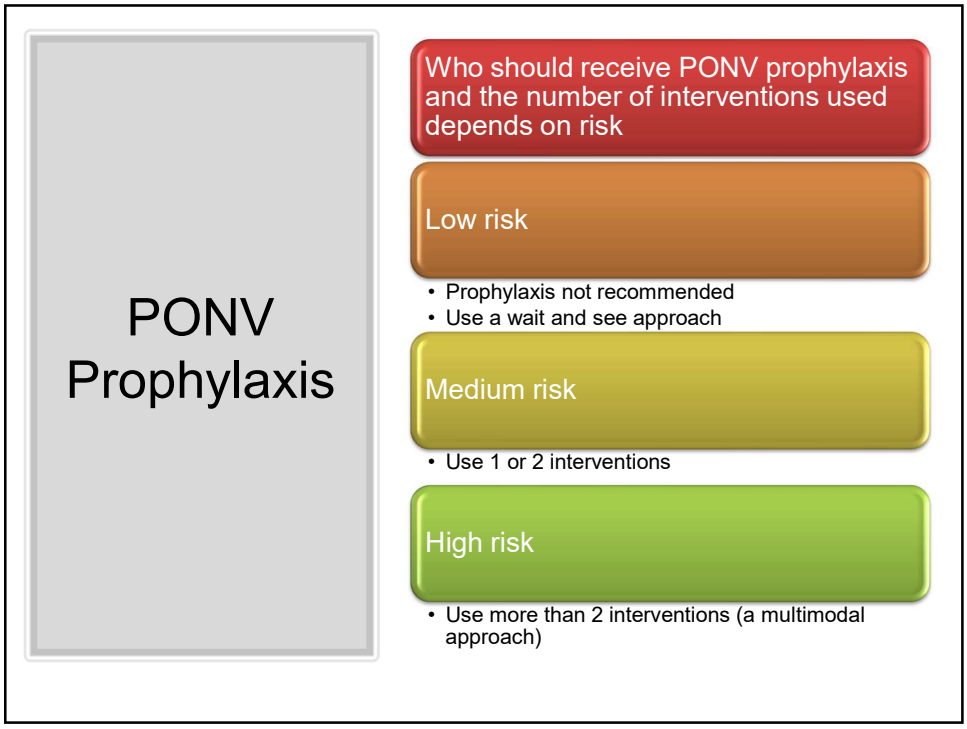

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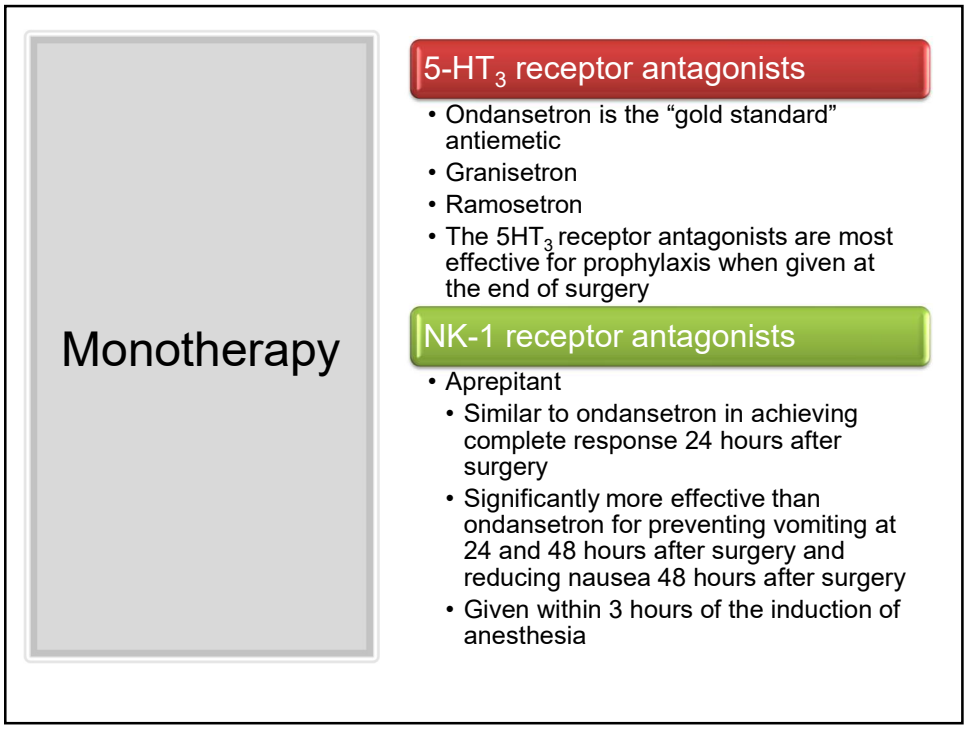

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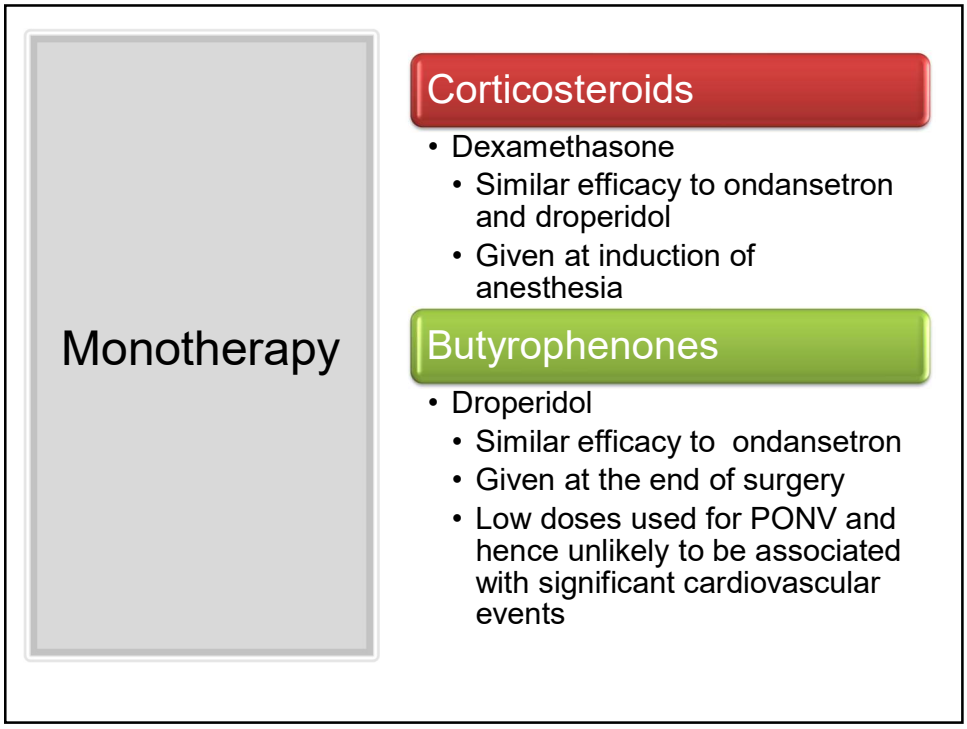

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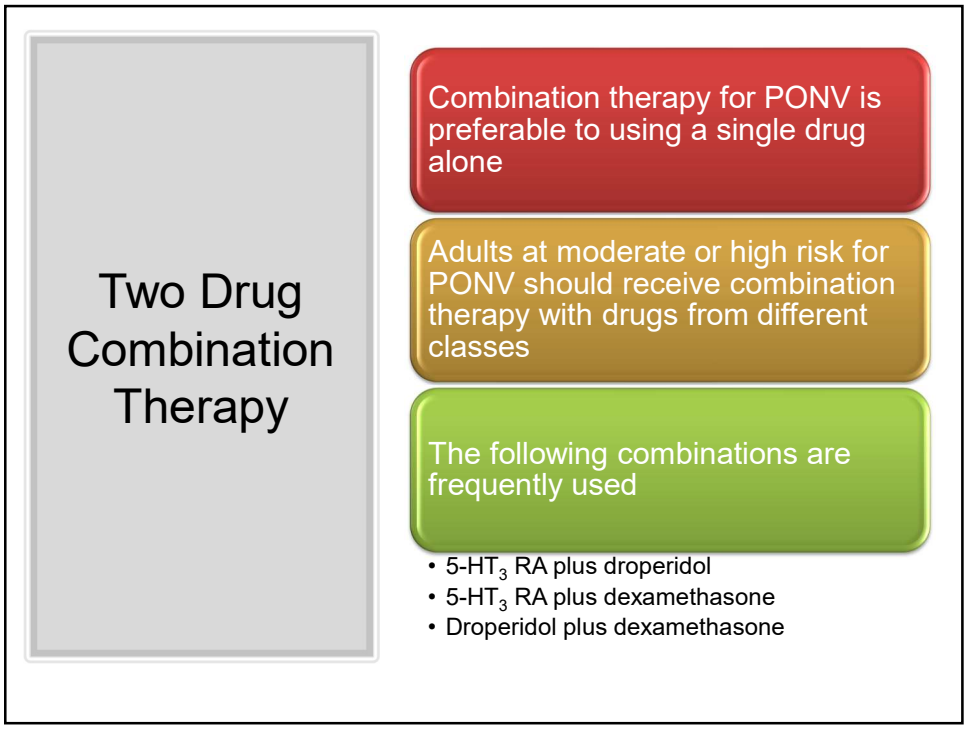

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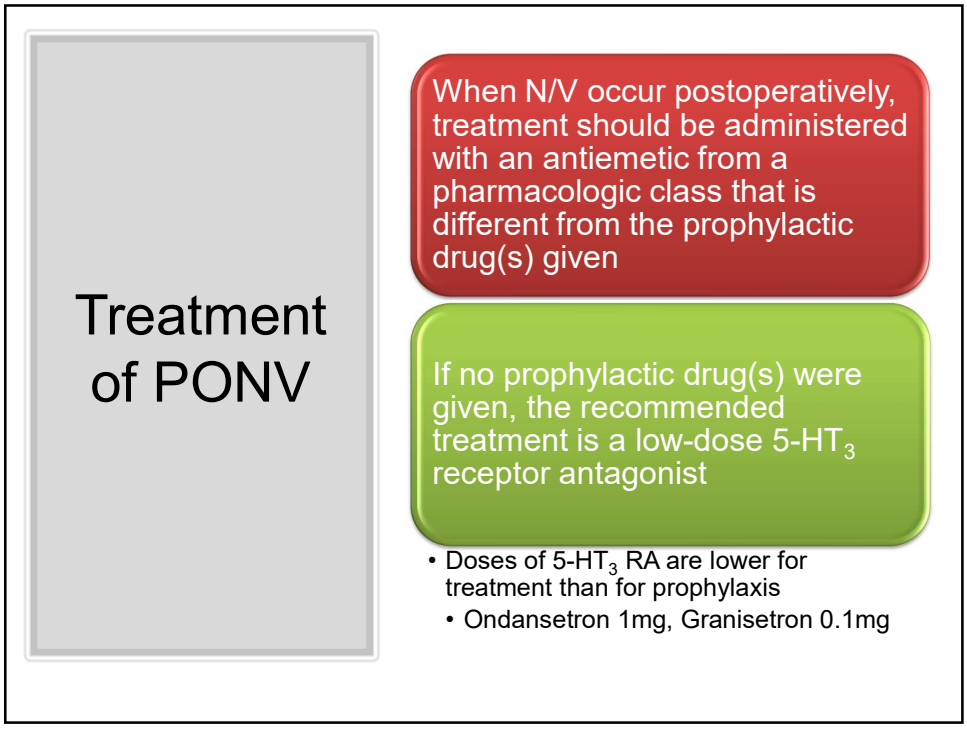

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Treatment of N/V in Disorders of Balance

Disorders of balance include vertigo, dizziness, and motion sickness

Antihistaminergic-Anticholinergic agents work best

Give medication prior to motion

- They are thought to act as vestibular depressants and hence can help decrease vertigo in addition to nausea and vomiting

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H_1 antagonist

meclizine (Antivert®) OTC

- 25 mg Given 1 hour prior to travel or every 12-24 hours as needed

diphenhydramine (Benadryl®) OTC

- 25-50 mg po q6h prn (max 400mg)
- Liquid available

hydroxyzine (Atarax®) RX

- 25-50 mg po q6h prn

dimenhydrinate (Dramamine®) OTC

- 50-100 mg po, IV/IM q4h prn (max 400mg)

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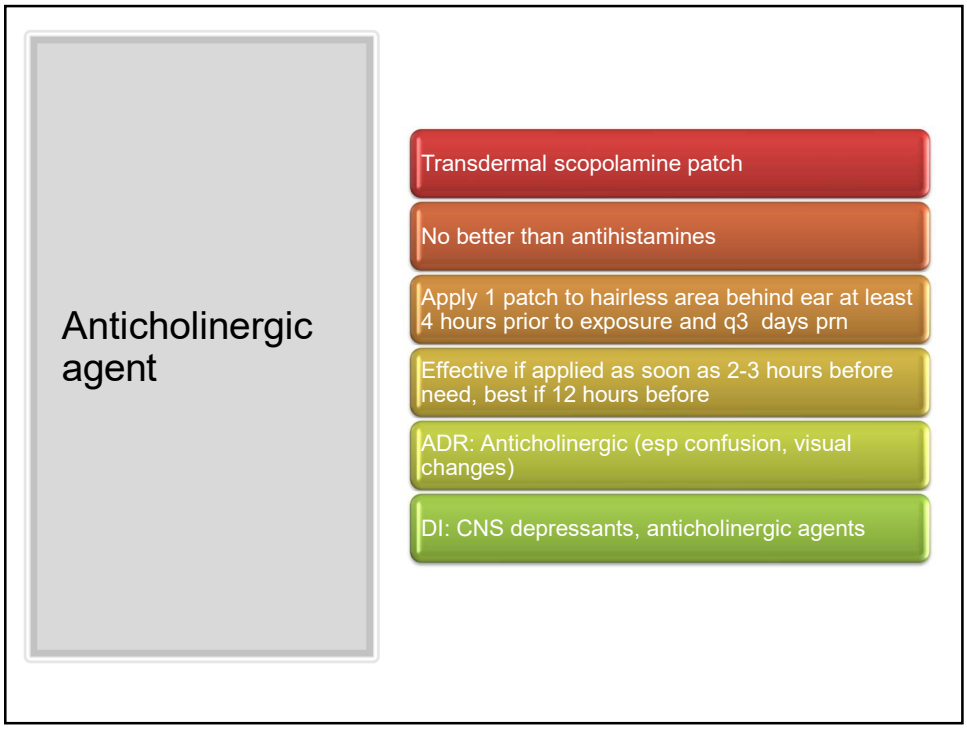

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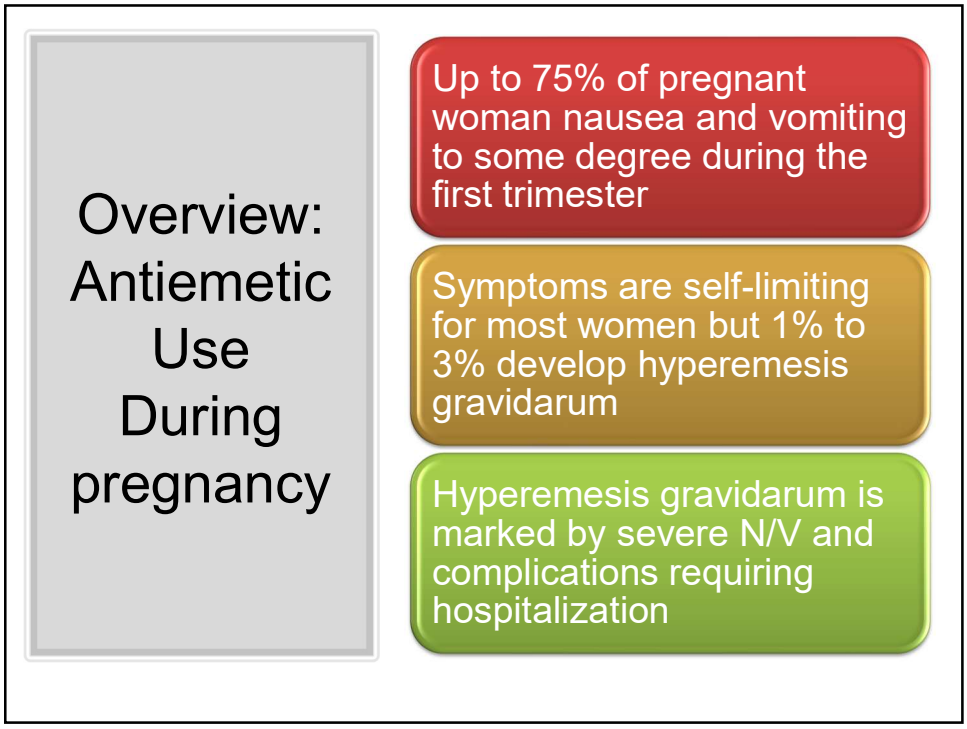

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Prevention and Treatment (Mild N/V in Pregnancy)

Taking prenatal vitamins for 3 months prior to conception may reduce the incidence and severity of N/V in pregnancy

First-line therapy for treatment

- Pyridoxine (10-25 mg 1-4 times daily) with or without doxylamine (12.5-20 mg 1-4 times daily)
- Diclegis® - cost - $627 for 100 tablets
- Can acquire each separately OTC or the combination by prescription

Treatment with ginger has shown benefit in reducing nausea and can be considered a nonpharmacologic option

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Treatment of Severe N/V in Pregnancy or Hyperemesis Gravidarum

If dehydrated, the patient should receive IV fluid replacement with thiamine

Ondansetron

- 2-8 mg orally/IV every 8 mg daily
  - Avoid in first trimester if possible (Cat B)
  - Increased risk for cleft palate
  - QT prolongation

For refractory cases, can treat with methylprednisolone

- 16 mg orally/IV every 8 hours for 3 days then taper for two weeks
- No more than 6 weeks therapy
- Cat C (D in first trimester)
- Increased risk of still birth and other forms of teratogenecity

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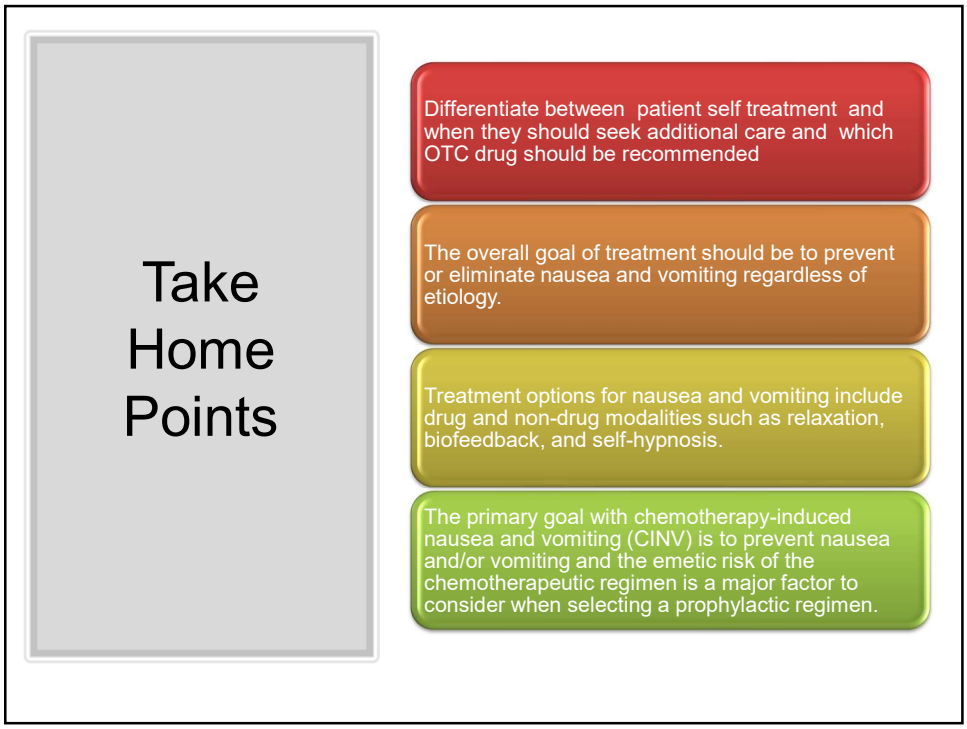

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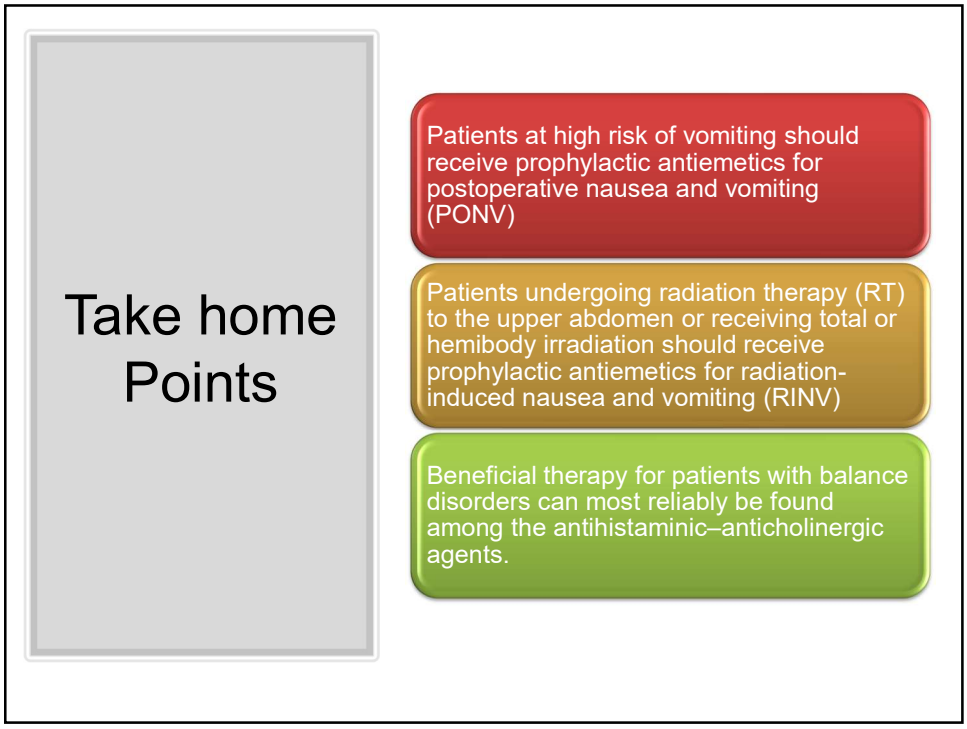

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